

Health status of ayahuasca users

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Ayahuasca is a psychedelic brew originally used for magico-religious purposes by Amerindian populations of the western Amazon Basin. Throughout the last four decades, the use of ayahuasca spread towards major cities in all regions of Brazil and abroad. This trend has raised concerns that regular use of this *N,N*-dimethyltryptamine- and harmala-alkaloid-containing tea may lead to mental and physical health problems associated typically with drug abuse. To further elucidate the mental and physical health of ayahuasca users, we conducted a literature search in the international medical PubMed database. Inclusion criteria were evaluation of any related effect of ayahuasca use that occurred after the resolution of acute effects of the brew. Fifteen publications were related to emotional, cognitive, and physical health of ayahuasca users. The accumulated data suggest that ayahuasca use is safe and may even be, under certain conditions, beneficial. However, methodological bias of the reviewed studies might have contributed to the preponderance of beneficial effects and to the few adverse effects reported. The data up to now do not appear to allow for definitive conclusions to be drawn on the effects of ayahuasca use on mental and physical health, but some studies point in the direction of beneficial effects. Additional studies are suggested to provide further clarification. Copyright © 2012 John Wiley & Sons, Ltd.

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Introduction

Ayahuasca is the name given to a decoction of various plant extracts containing *N,N*-dimethyltryptamine (DMT) and β -carboline alkaloids such as harmine, harmaline, and tetrahydroharmine.^[1] DMT is a classical tryptamine psychedelic which is thought to act primarily at 5HT_{2A}, 5HT_{2C}, and 5HT_{1A} receptors. DMT is psychoactive when injected or smoked, but when taken orally, it is metabolized rapidly by monoamine oxidase activity, (MAO-A) in the gastrointestinal tract. The β -carboline alkaloids harmine, tetrahydroharmine (THH) and harmaline present in the ayahuasca brew have monoamine oxidase inhibitor (MAOI) activity which renders DMT psychoactive via the oral route. In a typical ayahuasca brew, leaves of the shrub *Psychotria viridis* (containing DMT) and the vine *Banisteriopsis caapi* (containing β -carbolines) are boiled for several hours in order to extract the psychoactive constituents and to produce a viscous brew.

Acute subjective effects of ayahuasca include stimulation as well as perceptual, cognitive, affective and kinesthetic alterations^[2] which follow a classic dose–response pattern.^[3,4] Numinousness, personal and religious insights, and peaceful states are also described as prominent effects of ayahuasca. Unpleasant reactions such as acute anxiety may occur.^[5,6] The onset of effects begins 30 to 60 min after ingestion, reaching maximum intensity between 60 and 120 min, with a return to baseline by 4 to 6 h.^[2–4] Regarding pharmacokinetics, β -carboline alkaloids' plasma concentrations peak later than DMT, with THH showing a markedly longer course than the other ayahuasca alkaloids.^[2,7–10] Cardiovascular responses (i.e. beats per minute and systolic/diastolic blood pressure) elicited during the acute effects of ayahuasca are moderate, relatively safe, and milder than those reported for more prototypical sympathomimetic drugs such as amphetamine, and most psychological and

physiological parameters return to baseline within 6 h following ayahuasca intake.^[3,8,10]

Archeological data suggest its use in Amazonian pre-Columbian cultures may date to 2000 BC.^[11] Contemporary culturally sanctioned ritual use of the brew for magic-religious purposes throughout the western Amazon Basin by Amerindian and mestizo populations (i.e. mixed indigenous and non-indigenous) has been described.^[12–14] Ethnological studies suggest that the rituals use of ayahuasca in these societies can minimize social and psychological problems associated with the abuse of psychoactive substances observed in western societies.^[15]

Throughout the last 35 years, the use of ayahuasca has spread from the Amazon rainforest into urban settings in all regions of Brazil and parts of Europe, Japan, Canada, and the USA. This phenomenon is the consequence of the expansion of formal ayahuasca religions, such as União do Vegetal (UDV) and Santo Daime (especially the Santo Daime Branch called Centro Flúente Luz Universal Raimundo Irineu Serra – CEFLURIS), and the popularization of ayahuasca use within a more independent context.^[16,17] This expanded use of ayahuasca brought various religious ayahuasca groups under scrutiny by government officials around the world, in part because DMT is classified as a controlled

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substance.^[18] In Brazil, a federal interdisciplinary regulatory commission upheld a favourable decision for the religious use of ayahuasca.^[19,20] A similar official initiative allowed for the Santo Daime activities in Canada.^[17] In Holland, Santo Daime was legally allowed to conduct its ayahuasca ceremonies after winning a lawsuit in 2001.^[21] In 2006, the US Supreme Court affirmed the right of the UDV to possess and use ayahuasca in their religious ceremonies.^[22,23] In 2009, the District Court of Oregon similarly ruled in favour of the local Santo Daime community.^[24] It is noteworthy, however, that these judicial decisions were based on a minimum of scientific evidence concerning the effects of ayahuasca, since so few rigorous studies of long-term safety and/or persisting effects exist.^[23] While there is value in studying the phenomenology and mechanisms of acute effects, those seen days to years after ayahuasca intake are more relevant to regarding functional significance, both positive and negative. This paper addresses these concerns by means of a systematic review of the scientific literature regarding longer-term effects of ayahuasca. We will highlight current findings and suggest directions for new future research.

Method

Using the keyword 'ayahuasca', we conducted a survey of the literature displayed in the PubMed database. Screening criteria for studies investigating physical and mental health in humans were: (1) reporting original data; (2) evaluation of individuals who used ayahuasca at least once in their lifetime; (3) evaluation of the dependent variables: functional health status, including emotional, cognitive, behavioural, social, and physical aspects; (4) evaluation of these dimensions no sooner than the resolution of the acute psychological ayahuasca effects (i.e. ≥ 6 h after dosing,^[10] and (5) evaluation of ≥ 5 subjects.

Results

The literature search yielded 105 references published from 1953 to 2010 that were screened according to the criteria listed. Most studies were excluded because they fell outside the pre-defined inclusion criteria. These included reviews without original data, pharmacognosy and analytical studies, animal models, ethnographic and sociological research, and those which described only acute physiological and psychological effects in humans. Thus, 15 separate publications describing 10 different studies met our inclusion criteria. Table 1 shows the methods used to evaluate the persistent effects of ayahuasca. We divided our analyses of the findings into two major categories: The *quantitative data* section which displays data gathered through standardized instruments and *qualitative data* which display data gathered through non-standardized procedures, such as open-ended interviews.

Quantitative data

Alcohol/psychoactive drug-related problems

Five case-control and cross-sectional studies focused on the relationships between ayahuasca use and drug/alcohol in ayahuasca users. Grob *et al.*^[2] administered the Composite International Diagnostic Interview (CIDI) and reported no current drug/alcohol-related problems among adult ayahuasca users

compared to one subject with a current diagnosis of alcohol use disorder in non-ayahuasca-using controls. Interestingly, the authors found five subjects in the ayahuasca group formerly met criteria for alcohol use disorders but no longer met criteria after having become members of the UDV; this compared to only one such individual in the control group.

Doering-Silveira *et al.*^[25] found that adolescents who consumed ayahuasca in the UDV appeared to use less alcohol and amphetamine during a 30-day period before assessment compared to control subjects with no history of ayahuasca use. Halpern *et al.*^[26] administered the Structured Clinical Interview for DSM-IV psychiatric disorders and detected an individual with marijuana dependence in partial remission and another one with ongoing marijuana abuse in an ayahuasca-using sample of 32 individuals. However, 22 subjects had a history of drug/alcohol-related problems in full remission. Eight had met the criteria for alcohol abuse, five for alcohol dependence, four for marijuana abuse, three for marijuana dependence, three for hallucinogen abuse, and one each for hypnotic-sedative dependence, cocaine abuse, and stimulant abuse. All five subjects with history of alcohol dependence attributed their remission to the ayahuasca church process.

Fabregas *et al.*^[27] were going beyond the cross-sectional study design and administered the Addiction Severity Index 5th Edition (ASI) to evaluate alcohol and drug use in a community of long-term ayahuasca users within the Amazon jungle (CEFLURIS branch of Santo Daime) and among long-term urban ayahuasca users in Barquinha and other Santo Daime branches. Jungle and urban groups were evaluated twice, i.e. at baseline and at one year follow-up, and compared them with non-ayahuasca users. The authors reported lower alcohol use among the ayahuasca group in the Amazon jungle community at baseline and at one year follow-up, and in urban ayahuasca groups at baseline only, when compared to controls. However, ayahuasca groups reported greater use of psychoactive drugs than the controls at baseline and 1 year follow-up. The latter finding was interpreted as reflecting ayahuasca use being included in the drug scores in addition to the fact that *cannabis sativa* use is culturally, and religiously, sanctioned in the CEFLURIS jungle community. The authors also found a history of a significantly greater prior use of other drugs of abuse by members of the ayahuasca community than in the control group.

Kacic *et al.*^[28] surveyed 121 DMT users in Australia, out of which 37 had used DMT in ayahuasca brews and 119 had smoked DMT. They reported that 23% of the 37 subjects used ayahuasca along with other substances (including cannabis and psilocybin) and 68.1%, of 119 smoked DMT with other drugs use among users of smoked DMT (including cannabis, LSD, alcohol, psilocybin, and MDMA). It was also reported that ayahuasca users had smoked DMT on more occasions than ayahuasca-naïve DMT users. The authors speculated that this finding may have reflected a progression of a subset of DMT users towards ayahuasca which would be associated with subsequently less use of other drugs.

Psychiatric morbidity

Case-control and cross-sectional studies suggest that those who use ayahuasca in a religious setting demonstrate less psychiatric morbidity than non-ayahuasca using controls as well as the normative population data. Grob *et al.*^[2] reported that administration of CIDI identified no-one with current psychiatric

diagnoses in the UDV group compared to one with hypochondriasis in the control group. The CIDI also revealed two ayahuasca subjects with past histories of major depressive disorder and three with past phobic anxiety disorders. Fabregas *et al.*^[27] found significantly better scores on the psychiatric status subscale of the ASI among a jungle ayahuasca-using community at baseline and one year follow-up, and in urban ayahuasca groups at baseline only relative to their comparison groups. Da Silva *et al.*^[29] reported that ayahuasca-using adolescents in the UDV demonstrated better scores than non-ayahuasca using control subjects in measures of anxiety using the Beck Anxiety Inventory and STAI (State-Trait Anxiety Inventory), for body dysmorphism symptoms as assessed by Body Shape Questionnaire, and for Attention Deficit Disorder using Conner's Adolescent Self-Rating scale. All measures were comparable with the general population except for the high rate of depression in both the ayahuasca group (12/40) and comparison group (11/40), assessed through Center for Epidemiological Studies Depression Scale [CES-D].

Halpern *et al.*^[26] reported lower scores in Daime church members for symptoms of somatization, anxiety, depression, hostility, phobia, paranoid ideation, and psychoticism using the Symptom Check List Revised 90 (SCLR90) than a normative sample. These authors used no control group. Halpern *et al.* also reported similar scores in both for obsessive-compulsive and interpersonal sensitivity measures. Ayahuasca users scored better than normative data for the three SCLR90 measures that indicate overall symptomatology across the nine symptoms dimensions: Positive Symptom Total (i.e. Santo Daime subjects had fewer overall complaints), Positive Symptom Distress Index (i.e. less intensity of complaints), and Global Severity Index (i.e. lower levels of overall severity). Moreover, ayahuasca users were free of clinically significant anxiety (0/32) as measured by the Hamilton Anxiety Rating Scale, as well as demonstrating a low rate of depression (1/32) as measured by Hamilton Depression Rating Scale. Ayahuasca users showed no evidence of presumptive childhood ADHD (evaluated through the Wender Utah Rating Scale [WURS]) nor conduct disorder, and revealed well-adjusted lives as measured by the Uplifts, Hassles, Stresses, and Cognitive Failures questionnaire (UHSCF). Administration of the Structured Clinical Interview for DSM-IV Disorder (SCID) revealed that five subjects had a single major depressive disorder before joining Santo Daime. SCID also revealed the presence of one individual with a current bipolar I disorder, one with a current panic disorder, six with recurrent major depressive disorder with four in remission and two in partial remission, and two with simple phobia disorder in partial remission, four with simple phobia (two in remission and two in partial remission), three with bulimia nervosa in remission, six with post-traumatic stress disorder or panic disorder in remission. Eight subjects reported remission occurring after their involvement in ayahuasca religious use.

Barbosa *et al.*^[5,30] conducted a prospective study which evaluated psychiatric morbidity in new ayahuasca users. They administered the Clinical Interview Schedule – revised edition (CIS-R) to evaluate the intensity of minor psychiatric symptoms (e.g. anxiety, depression, depressive ideas, irritation) shortly before and one week after the first religious ayahuasca experience in Santo Daime ($n = 19$) or UDV ($n = 9$).^[5] This team re-administered the CIS-R in six-month later when 5 subjects (one from UDV and four from Santo Daime) were lost to follow-up.^[30] The Santo Daime sub-sample nearly met criteria for the CIS-R defined psychiatric disorder (12 or greater) before drinking ayahuasca and scores significantly improved at one week and six-month

follow-up (11.6 before ayahuasca, 5.1 a week later and six-months later). The UDV sub-sample scored below the cut off value for CIS-R defined psychiatric disorder before beginning participation and showed no significant changes at either one-week or six-month follow-up. Significant improvement in the mental health dimension of the Short Form-36 Health Survey Questionnaire (SF-36) was also demonstrated between baseline and six-month follow up in the Santo Daime group.

The authors also analyzed the differences between regular ayahuasca users, i.e. subjects who underwent more than nine ayahuasca experiences, and a washout period of four weeks or less before the last evaluation, and irregular ayahuasca users, i.e. subjects who underwent nine or less ayahuasca experiences and a washout period of more than four weeks before the last evaluation. At one-week follow-up regular ayahuasca users' CIS-R scores improved significantly and were significantly better than those of irregular ayahuasca users.

Personality

Personality variables related to the use of ayahuasca were investigated in one case-control study and in one prospective study. Grob *et al.*^[2] administered Cloninger's Tridimensional Personality Questionnaire (TPQ) to long-term ayahuasca users and non-ayahuasca using controls. The TPQ measures three dimensions of personality: Novelty Seeking, Reward Dependence and Harm Avoidance. The authors found lower scores for Novelty Seeking and Harm Avoidance in the ayahuasca group. The combination of lower Novelty Seeking and Harm Avoidance suggested that ayahuasca users were more reflective, rigid, slow-tempered, frugal, confident, relaxed, optimistic, and energetic than the controls.

Barbosa *et al.*^[30] used Cloninger's Temperament and Character Inventory – 125 items (TCI-125) which measures the same temperament dimensions as the TPQ plus additional domains of some specific character traits (Self-Directedness, Self-Transcendence and Cooperativeness) to evaluate effects on these traits in new ayahuasca users. The TCI was administered shortly before and six months after the first ayahuasca experience to new members of the Santo Daime ($n = 15$) or UDV ($n = 8$). There was no change in the Novelty Seeking domain between baseline and six months. Harm Avoidance scores dropped in the Santo Daime sub-sample which, in TCI model, means lowered anxiety-related behavioural traits. In addition, Reward Dependence decreased in the UDV sub-sample. According to this model, the lowering of reward dependence scores suggests a decrease in such behaviour: for example, from sentimentality, eagerness to please others, and sensitivity to signs of social approval towards detachment, coolness, emotional independence, and less sensitivity to signals of social approval. Change in Reward Dependence was positively correlated with the frequency of ayahuasca use, and negatively correlated with the length of time elapsing between the last ayahuasca session and re-testing. A positive correlation between the decrease in scores for Reward Dependence and intensity of ayahuasca use was also found in the total sample ($n = 23$). Regular ayahuasca users (i.e. those who attended more than nine ayahuasca sessions during the evaluation period) also showed a decrease in Reward Dependence. Regular users scored significantly higher than irregular users (i.e. those who attended nine or fewer ayahuasca sessions during the evaluation period) on Reward Dependence at baseline and higher on Self-Directedness at the six-month evaluation.

Table 1. Methods used to evaluate the health status of ayahuasca users

Reference	N (male/female)	Age (mean-range)	Education	Nationality/ residence	Setting/Country/ State and city of ayahuasca intake	Dependent quantitative variables	Dependent qualitative variables	Intensity of use	Control	Evaluation time points (quantity, when)
Case-control studies with experienced ayahuasca users										
[33]	13 (13,0)	38.5 (28-48)	N.I.	Brazil	UDV/ Brazil/ AM/ Manaus	Density of platelet serotonin uptake sites	No	Church members ≥ 10 years (use ≥ twice a month)	10 matched subjects with no history of ayahuasca use	1
[2]	15 (15,0)	38.5 (28-48)	N.I.	Brazil	UDV/ Brazil/ AM/ Manaus	Psychiatric Dx Drug Use Personality Memory	Perceived effects	Idem	15 matched subjects with no history of ayahuasca use	1
[31]	40 (22,18)	Adolescents 16,5 (15-19)	1st year high school to 1st year college	Brazil	UDV/ Brazil/ SP e DF/ São Paulo e Brasília	Memory and attention processes	No	≥24 ayahuasca ritual attendance throughout the previous 2 yrs	40 matched subjects with no history of ayahuasca use	1
[29]	Idem	Idem	Idem	Brazil	Idem	Psychiatric morbidity	No	Idem	Idem	1
[25]	41 (N.I.)	Idem	Idem	Brazil	Idem	Drug use	No	Idem	43 matched subjects with no history of ayahuasca use	1
[36]	29 (N.I.)	(15-19)	N.I.	Brazil	Idem	No	Attitudes and psychosocial status	Idem	25 matched subjects with no history of ayahuasca use	1
[27]	127 (62,65)	37,1 (N.I.)	10.4 years (mean) formal education	Brazil	CEFLURIS, Alto Santo and Barquinha Barquinha/ AM e AC/ Céu do Mapiá e Rio Branco	Medical Status, Employment/ Support, Drug and Alcohol Use, Legal Status, Family/Social Relationships, and Psychiatric Status	No	Church members ≥ 15 years with a ritual attendance ≥ twice a month	115 controls non ayahuasca users	2, one yr apart
Prospective studies with new ayahuasca users										
[5]	28 (12,16)	35,7 (18-56)	Complete high school to complete college degree	Brazil	UDV and CEFLURIS/ Brazil/ SP/ São Paulo e Campinas	Psychiatric morbidity	Attitudes and perceived effects	New ayahuasca users: 1 ritual	Before-after	2 (1-4 days before and 1-2 weeks after the 1 st ritual)
[30]	23 (8,15)	37 (18-57)	Idem	Brazil	Idem	Psychiatric morbidity, Quality of life and personality	No	New ayahuasca users: 1- 10 rituals	Before-after	3 (1-4 days before, 1 week and 6 months after 1 st ritual)
[6]	49 (23,26)	33 (N.I.)	N.I.	USA/ Canada	Independent ritual in USA and Canada / San Francisco/ British Columbia	Spiritual wellbeing and mystical experience	Perceived effects on spirituality	New ayahuasca users: 1 ritual	Before-after and 5 controls with no history of ayahuasca use	5 (72 hrs before and 6-12 hrs, 1 week and 3 months after 1 st ritual)

Cross-sectional studies									
[26]	32 (15,17)	49.6 (32-67)	16.4 years (mean) formal education	USA	CEFLURIS/ USA/ Oregon/ Ashland	Psychiatric morbidity and drug use	Perceived effects	Church members: 269±314.7 rituals (mean) 20-1300 (range)	No 1
[28]	37 *	NI	NI	Australia	"Recreational use" and "ayahuasca ceremonies" **	Drug use ***	Perceived effects	4 (mean) 1-180 (range)	No 1
Clinical Double blind crossover study									
[32]	22 (22,0)	27.1 (20-38)	N.I.	Spain	Laboratory / Spain Barcelona	Subjective and objective (EEG, EOG and EMG) sleep quality	No	1 standardized ayahuasca dose	Placebo e d- amphetamine 2 (before and between 11 and 19 hrs after dosing)
Qualitative phenomenological studies									
[34]	19 (11, 5)	45.1 (26-71)	N.I.	9 North-Americans and Canadians, 5 Europeans, 1 Venezuelan and 1 Japanese	Independent ritual in an Amazonian retreat	No	Motivations to try ayahuasca and perceived effects	1 to "several" doses	No During the days of the retreat
[35]	25 (11.14)	43.6 (22-63)	N.I.	Northern Europeans	Some European and South American countries (N.I. specific settings)	No	Motivations to try ayahuasca and perceived effects	17 rituals (mean) and 1-70 (range)	No 1

* The total sample of this study was 121 subjects who had used DMT; 37 had used it in ayahuasca preparations.

** The authors state that the expression 'recreational use' means drug intake outside recognized religious institution such as Santo Daime and they recognize that this term may be a misnomer. According to them, 5% of the 121 subjects took DMT in ayahuasca ceremonies, which suggest that their 37 ayahuasca subjects took the brew in independent rituals or in amateur ways.

*** The authors also evaluated the demographic characteristics of DMT users, as well as the ways of obtaining, reasons for trying, location of usage and route of using this drug. However the lack of specific analysis for ayahuasca (i.e. they treated ayahuasca as a form of DMT use and so the ayahuasca data are blurred into the larger DMT data) prevented these methods and data from being reviewed in the current paper.

Psychosocial status and well-being

Psychosocial status and wellbeing have been evaluated in one case-control study with experienced ayahuasca users and two prospective studies with new ayahuasca users. Fabregas *et al.*^[27] found significantly better scores on ASI-assessed Medical Status in a jungle ayahuasca community at baseline and urban ayahuasca groups at one year follow-up than comparison groups. At baseline, urban ayahuasca users scored better on a Family/Social Relationships subscale and worse on an Employment/Support subscale. The prospective study of Barbosa *et al.*^[30] reported improvement in the Bodily Pain subscale of SF-36 in the UDV group at six-month follow-up. Before the first ayahuasca experience, UDV group scores were better than those of the Santo Daime group for the Social Functioning and emotional role dimensions. At six-month follow-up, regular users (i.e. those who attended more than 9 ayahuasca sessions during the follow-up period) scored better than irregular users (i.e. those who attended nine or fewer ayahuasca sessions during the evaluation period) in the dimensions of Emotional Role and Social Functioning. Trichter *et al.*^[6] compared spiritual well-being using the Spiritual Well-Being (SWB) Scale in new ayahuasca users in the San Francisco Bay area ($n=14$) and in British Columbia, Canada ($n=33$) with control with no history of ayahuasca use ($n=5$). Subjects were assessed 72 h before and 6–12 h, 1 week, and 3 months after their first ayahuasca ritual. Authors reported positive changes in the Canadian group only (at 6 h evaluation). The authors also reported a correlation between Spiritual Well-Being changes and intensity of peak ayahuasca effects.

Cognition

Cognitive processes related to ayahuasca use were investigated by two case-control studies with experienced ayahuasca users. Grob *et al.*^[2] evaluated memory functions of long-term adult ayahuasca users in the UDV compared to matched controls, using the WHO-UCLA Auditory Verbal Learning Test (WHO UCLA-AVLT). This test is designed to assess mild degrees of cognitive dysfunction and consists of several trials of recalling words read from lists of common items such as household objects. The authors detected better performance in ayahuasca users in the recall of words for the fifth learning trial.

Doering-Silveira *et al.*^[31] administered a comprehensive battery of neuropsychological tests to assess attention, psychomotor speed, verbal and visual abilities, memory, and mental flexibility in long term ayahuasca-using adolescents in UDV and compared their scores with those of non-ayahuasca using adolescents. Ayahuasca-using subjects performed worse than the controls in the second and fourth learning trials and demonstrated lower total scores for trials I–V of the WHO UCLA-AVLT. The authors point out that the raw scores of both groups in this specific test were within the average range of normative data of similar aged adolescents on a similar memory task.

Sleep

Sleep was evaluated through a double blind crossover study conducted by Barbanoj *et al.*^[32] The authors compared the effects of a standardized dose of ayahuasca to inactive placebo and *d*-amphetamine in subjective and objective (EEG) sleep measures. The treatments were administered at noon and sleep measures were conducted from 11:00 pm until 7:00 am of the next day. Compared to *d*-amphetamine treatment, ayahuasca did not

induce deterioration of sleep quality, but like *d*-amphetamine, it increased stage 2, decreased REM stage duration, and showed a trend to increased REM latency.

Platelet serotonin uptake sites

Callaway *et al.*^[33] reported an increased number of [³H]citalopram binding sites in the platelets of long-term ayahuasca drinkers compared to non-ayahuasca controls. They suggest that this difference may reflect differences in neuronal 5-HT uptake, and that it might be reflected in decreased 5-HT in the synaptic cleft in the absence of compensatory mechanisms.

Qualitative data

Motivations to use ayahuasca

Motivations to use ayahuasca were elicited in open interviews administered in one prospective study and in two qualitative and phenomenological studies.^[5,34,35] Most South American, North American, and European subjects were motivated by a desire for gaining personal and spiritual knowledge and development, including self-awareness, purpose and direction in life, examining inner and outer realities, equilibrium and spiritual relationships. In addition, they report a desire for healing; e.g., improvement of psychosocial and emotional problems, and abuse of drug/alcohol. Recreational use and curiosity were less often cited.^[5,35]

Perceived positive effects

Perceived positive effects of ayahuasca use within a formal religions setting have been reported by European, South and North American, and Australian subjects.^[2,5,26] Data have also been reported for independent ayahuasca rituals and retreats^[6,34] and in non-religious settings.^[28] These benefits include a wide array of existential, religious, cognitive and emotional, attitudinal, and moral changes, as well as physical health. Interestingly, subjects also reported less impulsivity and aggressiveness and greater empathy, compassion and respect for others. Regarding the latter aspect, Grob *et al.*'s subjects^[2] emphasized similar changes from previous violence and alcohol and drug use towards more pro-social attitudes and behaviour. Dobkin de Rios' study^[36] reported that UDV adolescents also seemed to have better family and social relationships than matched controls. An increased interest in a number of other spirituality topics, such as yoga and meditation were also reported by North-American and European subjects.^[6,35] However, longitudinal assessment indicated that these interests faded over time.^[6]

Perceived negative or side effects

Halpern *et al.*^[26] reported that subjects described poor sleep the night after an ayahuasca ritual, decreased memory for up to 1 day afterwards, and exhaustion that lasted up to 2 days post ingestion. Concerns about the legality of using ayahuasca in the USA and politics of Santo Daime group were disliked.^[26] A subject from Barbosa *et al.*'s study^[5] reported feeling worry during the week following her first and distressing ayahuasca experience.

Subjects' interpretation and evaluation of processes of change

Subjects' interpretations of the positive effects of ayahuasca included integration of personal insights experienced during acute effects and mystical experiences. They use such notions as ayahuasca being a 'friend' with whom one could work,^[34] or being a 'guide' or a 'teacher'.^[26] Psychological and physical catharsis as well as novel subjective experiences of physical processes have also been reported.^[6,28,35] UDV subjects from Grob *et al.*'s study^[2] emphasized the importance of the ritual context and social support network provided by the church.

Discussion

This review summarizes case-control, longitudinal, cross-sectional, double-blind clinical laboratory, and qualitative-phenomenological studies conducted with ayahuasca in human subjects. Samples came from South and North America, Western Europe, Australia, and Japan where subjects took ayahuasca in formal religions, independent rituals, and clinical research settings. A diverse array of data collection procedures involving quantitative and qualitative tools have been used to assess the health of ayahuasca users. In general, the few studies reviewed here failed to demonstrate deleterious effects of ayahuasca use on their subjects' selected psychological and physical parameters. Interestingly, ayahuasca subjects had similar or better scores than controls and/or the general population on measures of psychiatric morbidity, and psychosocial status, and well-being. Studies consistently showed fewer problems of ayahuasca users with alcohol-related problems. Qualitative studies reported respondents describing a wide array of subjective existential, religious, cognitive, emotional, attitudinal, moral and physical benefits. Some of the results of the studies suggest that ayahuasca may be beneficial to certain people, but missed methodology which allows for evaluation of causal relationships.

Pharmacologically, Callaway's report of increased platelet 5-HT transport^[33] may suggest similar changes occurring in the brain of ayahuasca users. Such changes might result in long-term modulation of the aminergic systems involved in mood regulation, impulsivity, and alcohol abuse.^[2,37] More recently, human and animal studies suggested that DMT and harmine exert specific effects on 5-HT and noradrenergic [(NA)] systems involving depression, hopelessness, and anxiety during the acute effects of ayahuasca.^[38–41] Future studies should assess the temporal and dosing parameters in ayahuasca vs. other psychotherapeutic medications' effects on selected disorders and the use of appropriate animal models in more clearly determining ayahuasca's potential anti-depressant or anxiolytic effects.

The panoply of reports of increased self-awareness, purpose in life, introspection, spirituality, and healthier worldview suggest that ayahuasca elicits a complex series of psychological and social processes that can be considered independently of its pharmacology. Such data underline the importance of 'set and setting' in any psychedelic drug experience.^[42,43] Those with positive expectations and thorough preparation, support and follow-up may optimize effects of the drug on associative memory, mood, and other functions to effect potential emotional, personal, religious and moral benefits. The results of psychiatric studies with these in more easily controlled environments support this suggestion.^[44–46] Most of the reviewed studies involved subjects who took ayahuasca within structured formal religions or independent ceremonies. In addition, they also were

motivated by an interest in personal development and healing rather than recreation or curiosity. Thus, set and setting appear critical in our interpretation of our review of the 'field' literature in much the same manner as that established by experimental and psychotherapeutic studies of psychedelics.

Similarly, the anthropological literature^[47,48] posits ayahuasca religions' beliefs and practices direct the experience typically induced by ayahuasca towards positive social and individual outcomes by means of the collective ceremonial performance and guidance from religious leaders. The religious model used in many ayahuasca rituals suggests that cross-cultural sensitivity is necessary in studying its use, similar to that involved with research into peyote's comparable role in the Native American Church.

Two studies^[2,30] evaluating personality dimensions suggest that religious use of ayahuasca may result in changes in personality. Grob *et al.*'s^[2] finding of lower scores of Harm Avoidance among UDV members compared to control group and Barbosa *et al.*'s^[30] Ethnographic studies has described UDV as highly centralized and hierarchical, and requires following the most strict moral guidelines.^[49] These factors may have determined Grob *et al.*'s^[2] findings of lower novelty seeking scores in UDV subjects than the controls. It is uncertain which factors mediated Barbosa *et al.*'s^[30] finding of lowering of TCI-measured Reward Dependence on new ayahuasca users at six-month follow-up. The recent laboratory findings of psychedelic-induced personality changes suggest that ayahuasca itself may have contributed to these findings.^[50] While these results must require replication, they are of great interest given the high stability of personality traits under most circumstances.

More research is needed to determine whether ayahuasca use has significant effects on cognition. The superior performance of adult ayahuasca group compared to controls in Grob *et al.*'s study suggests that the regular religious use of the brew is without adverse effects in adults, but the data in adolescence is less benign.^[31]

There are few reports of adverse effects of ayahuasca in the literature. The exception is Halpern *et al.*'s study^[26] but this must be interpreted in light of Santo Daime rituals themselves. Participants are usually required to dance and sing for 8–12 h overnight and this may contribute as much to the impaired memory, exhaustion, and poor sleep the following days as the ayahuasca itself. In support of this interpretation are Barbanog *et al.*'s^[32] data demonstrating minimal effects of ayahuasca on sleep. It seems possible that this is a residual outcome of the over stimulation experience of dancing and listening to the hymns under the psychedelic effects. Of the reviewed papers, only Barbosa *et al.*^[5] found an emotional discomfort that outlasted a distressing ritual ayahuasca experience in one participant. Persisting psychological adverse reactions due to psychedelic use are more likely to happen when these substances are taken in unsupervised and unstructured settings.

The rarity of the persisting psychological reactions in the reviewed data might be explained by the fact that most of the studies focused on the use of ayahuasca within structured settings, where screening, preparation, supervision, and follow-up are provided, thus minimizing adverse effects.^[51,52]

In addition, selection-bias may play a role in the relative paucity of reports of adverse effects in the reviewed literature. Most subjects were experienced ayahuasca users who were evaluated in case-control and cross-sectional studies. It is expected from prior evidence that adverse reactions occur in the earlier

phases of ayahuasca exposition and people who undergo these kind of reaction tend to discontinue the use. Evidence of this selection bias was provided in the finding that new ayahuasca users who had better emotional outcomes during the week after their first ayahuasca attended more ayahuasca ceremonies throughout the following six months than those who had less beneficial emotional outcomes.^[30] Moreover, well-motivated subjects eager to prove that their psychoactive sacrament is beneficial may have contributed to the positive instrument scores and reports on ayahuasca effects. Finally, it has been hypothesized that the taste for an exotic experience and the desire to escape from the boredom of daily life might have contributed to wishful and superficial positive qualitative reports from new ayahuasca users that may not reflect consistent and persisting behavioural change.^[5]

Future studies should assess reasons for dropping out ayahuasca religions. Additional prospective evaluations of new ayahuasca users are necessary, as are retrospective assessments of patients in psychiatric facilities to determine the role of ayahuasca in their psychiatric complaints. Special attention should be given to psychotic reactions that outlast the acute ayahuasca effects, which has been reported in case studies and anecdotal reports.^[53,54] De Rios and Rumrill's ethnography on ayahuasca use by western subjects in the Amazon suggest that persisting psychological disturbances related to administration of ayahuasca by independent healers^[55] are far more frequent than in more structured formal ayahuasca religions. The growing use of ayahuasca within formal ayahuasca religions and in more independent contexts such as autonomous healers and recreational use provides an interesting opportunity investigate the role of different settings on frequency of both positive and negative persisting outcomes. Also, some remarkable differences between formal ayahuasca religions, such as the incorporation of cannabis in the rituals of CEFLURIS and the UDV rigorous proscription against marijuana, should be operationalized as independent variables in comparative evaluation of their members' psychological and well-being statuses. Finally, ayahuasca use is spreading to societies in which the prescription of selective serotonin reuptake inhibitors (SSRIs) medications is growing. The interaction of the MAOIs activity of ayahuasca with SSRIs can result in severe serotonergic syndrome characterized by nausea, confusion, tremors, vomiting, convulsions, loss of consciousness and is potentially fatal.^[56] Further studies should address the consequences and sequelae of interaction between SSRIs and ayahuasca.

Another significant gap in the reviewed studies is the lack of knowledge regarding the dose of DMT and beta-carbolines used by subjects. Fourteen of the 15 reviewed papers provided no data in this regard. Future studies should address this crucial variable. Analyses of various ayahuasca brews has demonstrated a rather spread of alkaloid concentrations.^[57]

In addition, nearly every study suffers from small sample sizes and most of lack a prospective design (i.e. evaluation of subjects before their exposure to ayahuasca), making difficult demonstration of causality between ayahuasca use and changes in dependent variables. Therefore, the benefits observed in the studies should be viewed with extreme caution, for case-control and cross-sectional designs suffer from an important methodological weakness to establish which factors mediated the observed results. In the few prospective studies with new ayahuasca users, the absence or small size of control groups^[5,6,30] make it difficult to determine the influence of unknown factors intervening between evaluations.

At a technical level, many of the neuropsychological and psychological instruments used in Brazil^[2,30,31] were adapted to

Brazilian Portuguese, but were not validated and have not been normalized in that country.

Nevertheless, observational studies have the advantage of evaluating ayahuasca use as it occurs in the real world and thus are crucial to public health issues regarding ayahuasca. The diversity of settings in which ayahuasca is being used present a unique opportunity for studying the effects of set and setting on the outcomes of the ayahuasca experience. International and cross-cultural studies will shed light on the complex interplay of these various factors.

Conclusion

We reviewed 15 reports on the effects of ayahuasca on health-related effects of ayahuasca on humans. Ayahuasca subjects scored similarly or better than the control groups or normative data on most measures of substance use, psychiatric morbidity, personality, wellbeing and cognitive functions when compared to control groups or population norms. The few significant exceptions were the worse scores drug-abuse related problems among Santo Daime and Barquinha subjects in Fabregas study and the worse scores the scores on memory subtasks of UDV adolescents than their controls. The former is explained by the option of the research team to take into account ayahuasca in the ASI score. As for the UDV adolescents, their raw scores in those subtests were within the norm range of a similar test. Moreover, predominant positive outcomes were elicited by qualitative interviews and questionnaires. Rare adverse effects were reported. These predominantly favourable results seem to be explained by the protective factors of the setting in which the most subjects drank the brew. Also, selection-bias, well-motivated subjects, and wishful thinking also may have biased the overall results towards positive outcomes. Finally, the causality of these results and ayahuasca intake is still an open question, for most studies lack retrospective data, and the few prospective studies that were conducted with new ayahuasca users suffers from small sample, which difficult generalization. More prospective studies are needed. Transcultural studies addressing the use of ayahuasca in different settings and addressing its adverse effects are needed to better understand the impact of the brew on human health.

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